U.PORTO
INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR
UNIVERSIDADE DO PORTO

Pediatric Psoriasis

Dissertação | Revisão Bibliográfica

Autor: Maria Vieira Relvas

Orientador: Dr. Tiago Torres

Dissertação – Artigo de Revisão Bibliográfica

Mestrado Integrado em Medicina
Ano Letivo 2015/2016

Pediatric Psoriasis

Autor: Maria Vieira Relvas, Estudante do 6º ano do Mestrado Integrado em Medicina no Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto.
Correspondência: mariavrelvas@gmail.com

Orientador: Dr. Tiago Torres, Assistente Hospitalar de Dermatologia e Venereologia e Responsável pela Consulta de Psoríase do Serviço de Dermatologia do Centro Hospitalar do Porto, Assistente de Dermatologia do Mestrado Integrado em Medicina - Instituto de Ciências Biomédicas Abel Salazar - Universidade do Porto.

Contents

AGRADECIMENTOS 4

RESUMO ALARGADO 5

ABSTRACT 13

INTRODUCTION 14

EPIDEMIOLOGY 15

PATHOGENESIS 16

CLINICAL FEATURES 18

DIAGNOSIS 23

DIFFERENTIAL DIAGNOSIS 25

COMORBIDITIES AND QUALITY OF LIFE IMPACT 27

TREATMENT 29

TOPICAL THERAPIES 29
PHOTOTHERAPY 31
SYSTEMIC THERAPIES 32
BIOLOGIC THERAPIES 34

CONCLUSION 36

REFERENCES 37

Agradecimentos

Quero expressar a minha enorme gratidão ao Dr. Tiago Torres, antes de mais por ter aceitado orientar a minha tese de Mestrado, mas principalmente pela sua inexcedível disponibilidade, interesse e genuína preocupação.

Ao meu tio Luís, queria agradecer pelo seu indispensável contributo para a revisão desta dissertação.

Não posso também deixar de agradecer aos meus pais por todo o apoio prestado, não só nesta última fase, mas ao longo destes seis anos de curso.

Por fim, ao meu namorado, uma palavra de reconhecimento pelo apoio incondicional de todos os dias.

Resumo Alargado

O objeto da presente dissertação, a psoríase, vê hoje ser-lhe reconhecida uma complexidade que extravasa a de uma simples doença inflamatória cutânea crónica, uma vez que, embora afete primariamente a pele, são-lhe associadas múltiplas comorbilidades que permitem a sua categorização como uma condição inflamatória sistémica crónica. Todavia, cumpre batalhar a visão da criança como um *pequeno adulto*, destrinçando e coletando informação concisa no que toca à sua particular epidemiologia, manifestações clínicas, diagnóstico e tratamento.

O resumo de seguida apresentado orienta-se segundo a estrutura adotada para a dissertação ora desenvolvida.

Epidemiologia

Estima-se que a psoríase afete entre 1-3% da população mundial, números que têm vindo sustentadamente a aumentar nos últimos quarenta anos, ainda que a sua prevalência seja altamente varíavel, contribuindo para este efeito fatores genéticos e ambientais, tais como idade, sexo, raça, etnia e localização geográfica.

Realce-se que cerca de um terço dos casos surgem ainda em idade pediátrica, mais especificamente entre os 8 e os 11 anos, apesar do diagnóstico, em muitos casos, ser obtido apenas em idade adulta. Porém, ao contrário daquilo que se observa em adultos, não é possível concluir por uma prevalência similar em ambos os sexos, uma vez que foram já apresentados estudos que demonstram uma ligeira predominância em crianças do sexo feminino. Por outro prisma, no que diz respeito a diferenças baseadas na raça, as crianças caucasianas são as mais afetadas quando em comparação com outras raças ou etnias, revelando também um início de sintomas numa idade mais precoce, o que poderá ser explicado por variações genéticas. Acrescente-se ainda que, cerca de 0,71% das crianças europeias sofrem da doença, enquanto no continente asiático a psoríase é praticamente inexistente.

Fisiopatologia

Os tempos mais recentes têm trazido avanços significativos que permitem, atualmente, uma melhor compreensão da fisiopatologia da psoríase, desde logo, sabendo-se agora que uma resposta inadequada por parte dos sistemas imunitários inato e adquirido, conjungada com fatores genéticos e ambientais, poderá ser a base da doença.

No que tange a fatores genéticos, calcula-se que aproximadamente 30% dos doentes tenham um familiar de primeiro grau afetado. Na verdade, a influência destes fatores reflete-se não só na fisiopatologia como também no curso da doença. O alelo de suscetibilidade HLA-Cw6, não obstante ainda não se poder afirmar com exatidão se constitui um alelo MHC clássico ou uma variante regulatória, é aquele com maior importância encontrado no locus PSORS1, acreditando-se que pode ter um papel fulcral na determinação de um início precoce da psoríase. Para além do exposto, os seus portadores possuem com maior frequência uma história familiar positiva e uma maior gravidade da doença. Com efeito, este alelo está fortemente relacionado com um tipo de psoríase específico, a psoríase gutata. Muitos outros genes associados a psoríase têm sido descritos, sendo que, à luz das investigações mais atuais, contam-se já cerca de 40, onde se incluem os genes codificadores da interleucina IL-12 e do recetor da interleucina IL-23 (IL-23R). Refira-se que estes genes em concreto são comuns a outras doenças inflamatórias, tais como colite ulcerosa (IL-23R) e doença de Chron (IL-12 e IL-23R).

Acredita-se que a interação entre queratinócitos e diferentes subtipos de células T, tais como Th-1, Th-17 e Th-22, seja a principal responsável para o desenvolvimento das lesões psoriáticas. Da mesma forma que os queratinócitos, as células dendríticas plasmocitóides, aumentadas na pele dos doentes com psoríase, libertam diversas citocinas, entre outras, a IL-23. O subtipo Th-17, particularmente importante na mediação da resposta inflamatória, conta com a ação desta interleucina sobre o seu recetor específico, IL-23R, para a sua diferenciação e ativação. Isto permite a libertação por parte destas células de citocinas cruciais implicadas na proliferação de queratinócitos, hiperplasia da epiderme e amplificação da inflamação.

Posto isto, são identificados diversos fatores desencadeadores da psoríase na população adulta, sendo muitos destes partilhados pelo doente pediátrico. O aparecimento de novas lesões psoriáticas pode ser precipitado, por exemplo, por traumatismo ou agentes irritantes, mecanismo este denominado Fenómeno de *Koebner*. Outros fatores ambientais que poderão originar lesões incluem: *stress* físico e emocional, que afeta especialmente a faixa etária em foco, tabagismo, fármacos e infeções, entre as quais se destacam as causadas por *Streptococcus* β-hemolítico dos grupos A, C e G.

Manifestações Clínicas

São reconhecidos diversos tipos de psoríase, sendo esta distinção feita com base na morfologia e localização das lesões, devendo realçar-se que a sua prevalência, bem como as suas manifestações clínicas no doente pediátrico, diferem ligeiramente das descritas em adultos.

A psoríase em placa, também denominada psoríase vulgar, apresenta-se como o tipo mais comum, afetando quase 70% dos doentes, que, no entanto, é um número substancialmente menor que os 90% de doentes afetados na população adulta. As lesões tendem também a ser menores, mais finas e menos descamativas, sendo o couro cabeludo um dos locais mais frequentemente afetados. A psoríase ungueal, podendo ocorrer associada a este tipo, assim como à artrite psoriática, ou até manifestar-se isoladamente, teve uma incidência de 39,2% nos casos implicados num estudo multicêntrico realizado em 2013 nos Estados Unidos América. Já na população adulta, na pendência do curso da doença, a psoríase ungueal atinge uma incidência de 80 a 90%.

A psoríase gutata constitui cerca de 30% dos casos em crianças, o que lhe atribui o estatuto de segundo tipo mais comum, sendo que se estima que um terço dos mesmos poderá desenvolver psoríase em placa mais tardiamente. Este tipo, em particular, é frequentemente precedido de uma infeção das vias respiratórias superiores ou região perianal causada pelo micro-organismo *Streptococcus* β-hemolítico, tendo sido reportada como fator desencadeador em 22,1% dos casos. Os restantes tipos de psoríase descritos, ocorrendo contudo num número muito inferior aos anteriormente enumerados, incluem: inversa, eritrodérmica, pustular, congénita, "nevoid-blackshoid" e psoríase na região da fralda. Destaca-se este último tipo, que ocorre exclusivamente em crianças, especialmente com idades inferiores a 2 anos, e que muitas vezes é erradamente diagnosticado como dermatite associada à fralda.

Diagnóstico e Diagnósticos Diferenciais

No âmbito do diagnóstico da psoríase, cumpre sublinhar que este é habitualmente estabelecido unicamente através de achados clínicos, sendo que a história familiar e potenciais fatores desencadeadores devem ser alvo de especial atenção por parte do médico. Destarte, uma minuciosa inspeção da pele, mucosas e unhas é indispensável, porquanto as características que mais fortemente sugerem o diagnóstico

englobam a ocorrência do Fenómeno de *Koebner*, o sinal de Auspitz, a existência de pigmentação residual após resolução das lesões e o *pitting* ungueal.

Por outro lado, quando existe a suspeita de uma infeção por *Streptococcus*, nomeadamente nos casos de psoríase gutata, deve ser recolhida uma amostra do local envolvido, através de zaragatoa e posteriormente enviada para exame microbiológico.

A somar ao exposto, dados relativos ao peso, altura e Índice de Massa Corporal devem também ser obtidos, adicionando-se a avaliação do perfil lipídico, glicemia em jejum e pressão arterial nos doentes em risco para síndrome metabólica. Por seu turno, a avaliação da gravidade da doença, bem como da eficácia terapêutica, é feita através do Índice de Área e Severidade da Psoríase (PASI – Psoriasis Area and Severity Index), sendo considerado o *gold-standard*. Contudo, alguns estudos recentes têm vindo a demonstrar que o produto entre a Avaliação Global do Médico (PGA – Physician Global Assessment, uma outra escala de medição de gravidade da doença) e a área de superfície corporal afetada, resulta numa alternativa ao PASI, tendo como principal vantagem o facto de ser bastante mais prática.

A presença de comorbilidades associadas à psoríase, assim como o seu impacto na qualidade de vida do doente, constituem dois importantes pontos aquando da avaliação da gravidade. Assim, o rastreio de doenças metabólicas, cardiovasculares e psicológicas é mandatório perante casos severos.

Em certos casos de psoríase, estabelecer o diagnóstico pode ser um verdadeiro desafio, atendendo à panóplia de condições inflamatórias e/ou infeciosas que devem ser consideradas como possíveis diagnósticos diferenciais. Não obstante, um dos diagnósticos diferenciais mais comuns, em qualquer tipo de psoríase, é o eczema, que poderá ser de diferentes tipos, tais como atópico, alérgico de contacto, numular ou desidrótico. Note-se que, recentemente, dois compostos presentes em muitas toalhitas higiénicas e antisépticos tópicos, a metilcloroisotiazolinona e a metilisotiazolina, foram identificados como os responsáveis pelo surgimento de dermatite alérgica de contacto na região perineal. Realce-se ainda outras condições inflamatórias, que incluem: dermatite seborreica, *pityriasis rosea, pityriasis rubra pilaris* e *lichen planus*. Por fim, relativamente a diagnósticos diferenciais de causa infeciosa, consideram-se candidíase, intertrigo bacteriano, sífilis secundária, *tinea corporis, tinea capitis* e onicomicose.

Comorbilidades e Impacto na qualidade de vida

A psoríase encontra-se associada a um conjunto considerável de comorbilidades que têm merecido o foco de diversos estudos realizados nos últimos anos, podendo hoje concluir-se que muitas das que são reconhecidas em adultos têm agora a sua ocorrência provada em crianças.

No seio das diversas comorbilidades identificadas, saliente-se que as doenças cardiovasculares e a síndrome metabólica são condições que contribuem para um aumento substancial de morbilidade nos doentes. Pese embora não estar plenamente comprovado, o conceito de *psoriatic march* tem sido proposto como uma possível explicação para a relação destas entidades com a psoríase. A inflamação sistémica presente na psoríase pode originar resistência aumentada à insulina, desencadeando uma disfunção celular epitelial, aterosclerose e por fim enfarte do miocárdio e acidente vascular cerebral. No mesmo sentido, dislipidemia, diabetes mellitus, hipertensão arterial e obesidade foram reportados como tendo uma prevalência duas vezes superior em crianças com psoríase, quando comparadas a controlos saudáveis. Desta feita, a psoríase pode mesmo constituir um fator de risco independente para a ocorrência de síndrome metabólica, alicerçando-se esta constatação num estudo que demonstra uma maior prevalência desta síndrome em crianças com psoríase em relação a controlos (30% vs 7,4%, respetivamente), ainda que uma diferença estatisticamente significativa entre os Índices de Massa Corporal das duas populações não tenha sido encontrada (22,7 e 22,3 para casos e controlos, respetivamente). Em consequência, poderá assim retirar-se uma possível explicação para o facto de, mesmo quando existe controlo adequado do peso e Índice de Massa Corporal, as crianças afetadas pela doença terem uma maior tendência para níveis lipídicos sanguíneos superiores e síndrome metabólica. Por outro lado, é possível encontrar outros estudos que elencam a obesidade como um fator desencadeador da psoríase, fundamentados na associação existente entre esta e um estado inflamatório sistémico, ainda que de baixo grau, devido à ação das adipocinas que resultam da interação entre macrófagos e adipócitos.

A psoríase pediátrica encontra-se igualmente associada a várias comorbilidades de carácter autoimune, sendo a artrite psoriática a que mais frequentemente se verifica. A sua prevalência em crianças que sofrem de psoríase ronda entre 1-10%, desenvolvendo-se cerca de uma década após o início dos sintomas cutâneos. Esta apresenta-se, inicialmente, como uma oligoartrite que afeta preferencialmente as pequenas articulações, tais como as interfalângicas dos membros superiores e inferiores,

mas que, posteriormente, pode também afetar articulações maiores. Aponte-se ainda a dactilite como uma manifestação clínica muito comum.

Por fim, e não menos importante que as comorbilidades previamente citadas, as consequências na saúde mental e na qualidade de vida do doente devem ser sempre avaliadas, uma vez que a psoríase, não raras vezes, resulta num impacto negativo de extrema relevância, especialmente nesta faixa etária. Um estudo comparativo entre doenças cutâneas e outras condições crónicas presentes na infância permitiu concluir que estas poderão causar uma diminuição na qualidade de vida tão elevada quanto a diabetes mellitus, a asma ou a epilepsia. A par da dermatite atópica, a psoríase foi mesmo a doença que mais impacto negativo registou, atendendo a que as lesões são percecionadas pela restante população, levando a que doenças cutâneas sejam propícias a que os seus portadores sejam vítimas de *bullying*.

Tratamento

No tocante à terapêutica da psoríase, uma parte considerável dos agentes farmacológicos utilizados nas crianças não foram ainda aprovados, requerendo, muitas vezes, uma prescrição *off-label.* Podemos assim constatar uma elevada carência de estudos de eficácia e segurança nesta população, nomeadamente, estudos que se debrucem sobre o *follow-up* e resultados a longo prazo. Por conseguinte, um considerável número de aspetos deve ser atendido na hora da tomada de decisão sobre um regime terapêutico em particular, incluindo a idade do doente, a gravidade da doença e o seu impacto na qualidade de vida, a morfologia e áreas de envolvimento das lesões, o custo e complexidade do tratamento, bem como aspetos práticos, tolerância e segurança, e, por fim, as preferências do doente. Atendendo a que a maioria das crianças sofre de doença leve a moderada, o tratamento tópico é normalmente o mais utilizado, reservando-se a fototerapia e os agentes sistémicos para casos severos ou refratários e, ainda, para aqueles com artrite psoriática ou reduzida qualidade de vida.

A respeito do primeiro, refira-se que a terapêutica tópica de primeira linha para qualquer tipo de psoríase inclui glucocorticoides, análogos da vitamina D_3 e inibidores da calcineurina, juntamente com queratolíticos como terapêutica adjuvante. Os agentes mais frequentemente prescritos são, indisputavelmente, os glucocorticoides, que existem numa enorme variedade de veículos e potências. Todavia, agentes de potência extremamente elevada devem ser utilizados com precaução ou até mesmo evitados em crianças, principalmente devido ao risco de absorção sistémica, resultante do maior

racio entre a superfície e massa corporal, que é superior nesta população. Atente-se também que estrias, telangiectasias, atrofia cutânea e supressão do eixo hipotalâmico-hipofisário-adrenal são os principais efeitos laterais resultantes de uma utilização contínua, pelo que, de modo a obter uma redução dos mesmos, os glucocorticoides são ocasionalmente combinados com outros agentes não-esteróides, como os análogos da vitamina D_3. Estes, para além de eficácia documentada em crianças, comportam adicionalmente um risco muito diminuído de efeitos laterais. Apesar de tudo, a absorção sistémica é, uma vez mais, um aspeto que deve ser tido em conta em doentes com terapia de longa duração ou com doença com extensa área de envolvimento, já que pode provocar alterações na concentração de cálcio sérico e, consequentemente, de fosfato e vitamina D. De modo a facilitar o seu uso por parte do doente e assim reduzir o incumprimento terapêutico, uma formulação de calcipotriol e dipropionato de betametasona encontra-se disponível, sendo a sua eficácia e segurança na população pediátrica descrita em diferentes estudos.

Além da aludida terapêuticia tópica, a fototerapia constitui um tratamento seguro e eficaz para crianças, sendo maioritariamente prescrito para casos de psoríase dos tipos em placa ou gutata, refratárias à terapêutica tópica, bem como em casos com envolvimento corporal difuso (mais de 15-20% de área de superfície corporal afetada) ou em doentes que não estejam indicados para terapêutica sistémica. Para este efeito consideram-se três tipos de radiação ultravioleta: UVA (320-400nm), UVB banda larga (290-320nm) e UVB banda estreita (311-330), sendo o último aquele que mais frequentemente é utilizado em crianças, uma vez que demonstrou obter bons resultados, em conjunto com efeitos laterais ligeiros.

Relativamente a terapêuticas sistémicas, tal como foi já referido, a informação disponível é escassa no que toca à eficácia e segurança do tratamento da psoríase na população pediátrica, pelo que a sua utilização baseia-se, muitas vezes, em dados respeitantes aos riscos e benefícios obtidos noutras doenças. Saliente-se que retinoides, metotrexato e ciclosporina, são os que mais habitualmente são prescritos, podendo, em determinados casos, ser combinados com terapêuticas tópicas.

Por sua vez, reservados para tratamento de segunda ou terceira linha, os agentes biológicos constituem terapêuticas atrativas e convenientes, devendo-se, em parte, a regimes de tratamento e monitorização mais simples quando comparados aos restantes agentes sistémicos. Apesar disso, não estão isentos de complicações, tais como a ocorrência de infeções oportunistas, neoplasias e reativação da tuberculose,

identificadas em doentes com artrite inflamatória juvenil tratados com estes agentes. Assim, o recurso a este tipo de tratamento deve ser restringido a casos severos e/ou refratários de psoríase em placa, gutata ou eritrodérmica, ou ainda a casos com artrite psoriática coexistente. Deste modo, para o tratamento da psoríase em crianças estão, atualmente, aprovados, pela European Medicines Agency, os inibidores do TNF-α, etarnecept e adalimumab, sendo que o primeiro pode ser utilizado em crianças com idade superior a 8 anos e o segundo numa idade superior a 4 anos. Recentemente, o ustekinumab, um anticorpo monoclonal contra a subunidade p40 das interleucinas IL-12 e IL-23, foi também aprovado para uso em crianças com idade superior a 12 anos.

É essencial focar a importância de um seguimento próximo e atento do doente pediátrico por parte do médico, cabendo-lhe informar e educar o doente e os seus progenitores ou encarregados de educação relativamente à doença, o que conduzirá, não só a um melhor cumprimento terapêutico, mas a uma qualidade de vida superior.

Apesar da grande quantidade de informação, que constantemente é atualizada, no que diz respeito a epidemiologia, manifestações clínicas, diagnóstico, e tratamento da psoríase, no doente pediátrico esta informação ainda não obteve o desenvolvimento desejável. Em consequência, muitos dos agentes terapêuticos aprovados em adultos não o estão para esta faixa etária por falta de estudos que comprovem a sua eficácia, segurança e efeitos a longo prazo.

A presente dissertação, baseada na pesquisa de estudos clínicos e artigos científicos através da base de dados MEDLINE - PubMed, tem como objetivo realizar uma revisão bibliográfica sobre a psoríase no doente pediátrico, mais concretamente nas vertentes da epidemiologia, fisiopatologia, manifestações clínicas, diagnóstico, comorbilidades e tratamento, procurando dar um contributo para um conhecimento mais sistemizado sobre esta temática.

Palavras-Chave: Psoríase; Pediatria; Doenças Cutâneas; Tratamento; Epidemiologia; Comorbilidades

Abstract

Psoriasis is one of the most relevant dermatologic conditions. Despite this, it is recognized as more than just a chronic inflammatory cutaneous disease. It is considered a chronic systemic inflammatory condition arising from a relationship between inadequate responses by innate and adaptive immune systems, genetics and several triggers and risk factors. It primarily affects the skin, but it is associated with several serious comorbidities.

Psoriasis is a relatively common condition, affecting between 1-3% of the population worldwide, numbers that have been increasing during the past forty years. There is a marked prevalence variation in which genetic and environmental factors such as age, gender, race, ethnicity and geographic location contribute. One-third of total psoriatic cases have their onset during pediatric age, although some of them may not be diagnosed until the patient reaches adulthood.

Since children are not just "small adults", specific guidelines for diagnosis, management and treatment are of extreme importance. Most of the treatments for psoriasis in adults, which are the same that are used in children, are not officially approved, requiring off-label prescription. Efficacy and safety studies are lacking in this population, especially the ones with long-term follow-up and outcomes.

This systematic review was written based on the research of clinical studies and scientific articles on psoriasis using MEDLINE - PubMed database. It intends to summarize the most relevant aspects, as well as updated information about the epidemiology, pathogenesis, clinical features, diagnosis, comorbidities and treatment of pediatric psoriasis.

Key-words: Psoriasis; Pediatrics; Skin Diseases; Treatment; Epidemiology; Comorbidities

Introduction

Psoriasis is currently recognized as more than just a chronic inflammatory cutaneous disease. It is considered a chronic systemic inflammatory condition primarily affecting the skin, but associated with several serious comorbidities that should not be forgotten.

One-third of all cases of psoriasis occur during pediatric age. Since children are not just “small adults”, specific guidelines for diagnosis, management and treatment are of extreme importance. An early recognition of the disease and a subsequent appropriate approach may delay or even prevent considerable comorbidities. At this particular age, even more than in adults, psoriasis can have a strong negative impact on quality of life, social relationships and school performance; therefore, a correct understanding of all the aspects of the disease in this particular age is of utmost concern.

This article provides a systematic review of characteristics of pediatric psoriasis, including epidemiology, pathogenesis, clinical features, diagnosis, comorbidities and treatment.

Epidemiology

Psoriasis is a relatively common condition, affecting between 1-3% of the population worldwide (2-4% of the European and North American population), numbers that have been increasing during the past forty years (1, 2). There is a marked prevalence variation in which genetic and environmental factors such as age, gender, race, ethnicity and geographic location (climate and sun exposure) contribute. Two clinical types of psoriasis can be considered relating to the age of onset: Type I – Early onset (≤ 40 years) and Type II – Late onset (> 40 years). Regarding type I, which accounts for 70% of all cases, the highest incidence rates are seen between 16 and 22 years, while on type II, the peak occurs amongst 57 and 60 years (3).

It is estimated that one-third of total psoriatic cases have their onset during pediatric age, although some of them may not be diagnosed until the patient reaches adulthood (1). Mean age of onset is 8 to 11 years old (4), with a higher incidence in the second decade of life (5). However, Augustin *et al* reported, in a large German study, an almost linear prevalence increase during all childhood, ranging from 0.12% at 1 year to 1-2% at 18 years (6), instead of having a "peak age of onset". With regards to gender, it is uncertain if the ratio between males and females is the same, since a minority of studies demonstrated a slightly higher incidence among female children, which is not observed in adult psoriasis (7, 8). Caucasian children are the most affected compared to the other races/ethnicities, revealing also an earlier mean age of onset (8), a fact that can be explained by genetic variances (see below). Around 0.71% of the children in Europe are affected, while in Asia, for example, psoriasis is almost absent (1, 8). In addition there is a correlation between latitude and incidence of the disease, increasing with the distance from the equator (7).

A positive family history of psoriasis in pediatric patients has been reported in several studies all around the world. It is estimated that about 30% of the patients have an affected first-degree member (9). If the family history correlates with the age of onset is still uncertain, since some studies show supportive results, while others do not (7, 10).

Pathogenesis

Recently, major advances have been made in understanding the pathogenesis of psoriasis. As stated before, psoriasis is a systemic inflammatory condition where the relationship amongst inadequate responses by innate and adaptive immune systems, genetics, several triggers and risk factors plays an important role.

Genetic factors are implied not only in psoriasis pathogenesis, but also in the course of the disease. Population studies suggest a higher incidence of psoriasis in first-degree and second-degree relatives of affected patients, with a five-fold increased risk of developing it (11), when compared to general population (12).

HLA-Cw6 is the most important susceptibility allele in psoriasis susceptibility locus 1, also known as PSORS1 (2), although it is still unknown if it is a classical MHC allele or a regulatory variant (13, 14). Certain is that this allele has a major role in determining an early-onset of psoriasis (15). Patients carrying it have a younger age of onset, more positive family history (16) and more extensive disease (3). In addition, it is strongly associated to guttate type (17) and more frequent exacerbations of the disease by throat infections (16, 18).

Several others psoriasis-associated genes have been described, numbering almost 40, according to the most recent research (2). These include IL-12 and IL-23 receptor (IL-23R) codifying genes; TNF-α-induced protein 3 (TNFAIP3) and TNFAIP3 interacting protein 1 (TNIP1) genes; and signal transducer and activator of transcription 2 (STAT2) gene (19), all playing a role in T-cell activity (19).

Some of these susceptibility loci may be shared with other inflammatory diseases: IL-23R by ulcerative colitis and IL-12 and IL-23R by Crohn's disease (19). In fact, in a study by Li Y *et al,* patients with Crohn's disease have been shown to be 5 times more likely to develop psoriasis than the general population (20).

Finally, generalized pustular psoriasis has been associated with a gain-of-function mutation in CARD14 gene (21), a member of the caspase recruitment family, and an IL-36 receptor antagonist deficiency (22).

It is believed that an interaction between keratinocytes and different T-cell subtypes, such as Th-1, Th-17 and Th-22, is the main responsible for the development of psoriatic lesions (1). Diverse effector cells, including neutrophils and plasmacytoid dendritic cells, activate T cells (23). Although being the most abundant type in the dermis, plasmacytoid dendritic cells, are augmented in psoriatic skin lesions (24). They

produce TNF-α, when activated by possible complexes of self-DNA and LL-37, an antimicrobial peptide, which is also overexpressed in psoriatic skin (25, 26). TNF-α, also produced by lymphocytes, keratinocytes and endothelial cells, has the ability to amplify inflammation through various pathways, inducing the synthesis and secretion of secondary mediators and adhesion molecules by distinct cells, implicated in psoriasis (27). In addition, dendritic cells, also release cytokines, including IL-23, that activate T cells and keratinocytes (23). A subset of T-cells, Th-17, is particularly important in mediating the inflammatory response in psoriasis. Their differentiation is mainly made by IL-23, when it interacts with IL-23 receptor, expressed in memory T-cells (28). Once activated they secret IL-17, IL-20, IL-22, IFN-γ and TNF-α, crucial cytokines implied in keratinocyte proliferation, epidermal hyperplasia and inflammation amplification (2, 29, 30). Keratinocytes, implied in pathogen recognition and antimicrobial peptides secretion (31), when activated by the referred cytokines, especially IL-17 and IL-22 (1), are involved in cytokine and chemokine production and subsequent increase of inflammatory cells at the affected skin site (32, 33).

This resulting inflammatory environment is auspicious for the proliferation of vascular endothelial cells and pro-angiogenic factors secretion (34), perpetuating the inflammation by facilitating the recruitment of circulating leucocytes to the skin (35).

Psoriasis triggers are better established in adult population than in pediatric patients, even so, both populations share some of them.

Skin trauma caused by injury or irritants may precipitate new psoriatic lesions, which is known as the Koebner Phenomenon (1). It consists of the appearance of isomorphic lesions after local trauma in previously normal skin sites (36). This stimulus however, does not cause psoriasis *per se*, neither induces illness in an individual who is not already susceptible (36). Other reported environmental triggers include: smoking, which is also associated with greater disease severity (37); physical and emotional stress, which especially affects pediatric patients (1), as a multicenter study made by Özden *et al* (2011) revealed (50.4% in the early-onset cases vs. 41.7% in the late-onset cases) (38); drugs, such as β-blockers and antimalarials (39, 40), as well as corticosteroids withdrawal (41); and infections.

Pharyngeal and perianal infection by groups A, C and G β-hemolytic streptococci, which all have M protein, is linked to the onset and exacerbation of guttate psoriasis (42). It is assumed to be triggered by cross-reactivity between skin and

inflammatory host cells and streptococcal antigens (43). In psoriatic patients, T-cells are implied in the recognition of streptococcal M proteins and keratin determinants (42), constituting a link between streptococcal tonsillitis and inflammation (44). Circulating Cutaneous Lymphocyte-associated Antigen $(CLA)^+$ T-cells are a subset of memory T-cells with skin tropism, associated with the cutaneous immune system (45). Ferran *et al* (2013) observed that mixing streptococcal throat extracts with CLA^+ T-cells and epidermal cells from psoriatic skin can lead to the production of IL-17, IL-21, IL-22 and IFN-γ, triggering a psoriatic immune response, as described above, and lesion development (46). In the same study, Anti-streptolysin O levels correlated with up-regulation of messenger RNA for three of those four mediators – IL-17, IL-22 and IFN-γ - plus IP-10, a potent chemokine expressed in psoriatic lesions (47). This suggests a higher activation of epidermal and CLA^+ T-cells in the setting of higher Anti-streptolysin O levels (46).

Lately, an association between obesity and the incidence of psoriasis in children has been established (29), making the former a possible risk factor for disease development (48). Two recent studies indicated that obesity may be a cause and not a consequence of psoriasis, since most of the patients presented with increased Body Mass Index preceding the disease onset (49, 50).

Clinical Features

Childhood psoriasis can be divided into several types. The distinction is based primarily on the shape and aspect of the lesions and sites of involvement. Their prevalence and clinical manifestations may however differ from the same types in adults.

- Plaque psoriasis, also known as *vulgaris*, is the most common type in children, affecting almost 70% of the patients (19), which is substantially less than in adults, where it accounts for about 90% (2). Characterized by monomorphic, erythematous plaques covered by micaceous lamellar scales (19), its presentation in children may be slightly different, with smaller, thinner and less scally lesions (5). Although it can occur in any site of the skin, scalp, forehead, face, post-auricular region, peri-umbilical area, buttocks and diaper area are the most affected (2, 19). Scalp involvement

was reported in 79% of the participants, at some time throughout the pediatric age, in a multicenter study realized in 2013 in United States (7). Usually it is the first site of involvement in children (51). The study also found out that girls tend to be more affected in this particular skin area (52). It shows up as thick adherent white scales, also called *tinea amiantacea*, which can lead to temporary loss of hair without leaving scar (1).

- Nail psoriasis presents, classically, as pitting, discoloration with yellow and brownish patches, onycholysis, subungual hyperkeratosis, onychodystrophy (Figure 1) and splinter hemorrages (10). Nail involvement, in the same multicenter study from 2013 referred above, reported an incidence, at some point, of 39.2% (1, 52), making it less frequent when compared to adults, where it reaches a life-time incidence of 80-90% (53). The same study showed a difference as regards to gender, with boys being more affected. Koebner Phenomenon might be the explanation for the disparity observed in nail and scalp incidence between both genders (52). Nail psoriasis can be associated with plaque psoriasis or psoriatic arthritis (PsA), or it can manifest by itself (19). Since the nail is as much an integral part of the entheseal unit as it is of the skin (54, 55), the ability to detect nail changes by dermatologists gives them a strategic role in the early detection of subclinical entheseal disease and in the referral and management of early PsA, thereby preventing severe, erosive and deforming joint lesions (56). Nail disease has been the most strongly associated clinical indicator for the prediction of PsA development (54). An incidence study that followed a cohort of 1593 psoriatic patients for thirty years, concluded that the ones with nail dystrophy were three times more likely to develop PsA, compared to the others without nail involvement (57).
- Guttate psoriasis constitutes around 30% of the cases in children (5, 19, 52), making this type the second most common (1). It is estimated that one-third of them may develop plaque-type later in life (58). It presents as localized, red-to-salmon coloured, small (less than 1 cm), round or oval plaques (reminding droplets, which explains the origin of the name), with hyperkeratosis (Figure 2). Lesions are usually found on the trunk, abdomen and back (Figures 3 and 4) (1, 19). This specific type is often preceded by a streptococcal infection of the upper respiratory tract or perianal area (59). A

study reported 22.1% of the guttate psoriasis cases having this infection as the initial trigger, making it much more common in children than in adults (52). Some other interesting findings relating to severity and family history were found: guttate type is seen more commonly in subjects with severe than mild disease, and is associated with a positive family history, being more often observed in children with affected first-degree relatives (52).

- Inverse psoriasis relates its name to the location of the lesions, which generally appear in flexural and intertriginous areas, including axillae (Figure 5) and groin. They manifest as erythematous, macerated, thick plaques, usually without scale, reflecting the friction and moisture of these areas (19). It can be associated with secondary infections by *Candida* or *Streptococcus*, which may require the usage of topical anti-infectives after positive cutaneous cultures (19).This type of psoriasis is more often seen in children than in adults (29).
- Erythrodermic psoriasis is a rare, but serious, life-threatening variant characterized by affecting more than 90% of the body surface area (2) with a generalized erythema and thickening of the skin. Fever, chills and malaise may be present. Bacteriemia is also a possible severe comorbidity that must be ruled out (19).
- Pustular psoriasis is a rare variant in children consisting of erythroderma accompanied by white, coalescing, sterile pustules (19). Five different types of pustular psoriasis may be distinguished (60): Generalized (or von Zumbusch), associated with sudden onset of fever and disseminated erythema; Localized, also known as palmo-plantar, affecting solely these areas; Annular, which is seen more frequently in children than in adults (61), characterized by elongated, annular, erythematous plaques with pustules and peripheral desquamation, that tend to spread; Psoriasis Vulgaris with Pustules; and Pustular Erythrodermic Psoriasis. Any type of psoriasis can become pustular (2).
- Diaper psoriasis, with the highest prevalence among children below 2 years of age, presents as a bright-red, well-demarcated, glazed rash of the groin folds and genital area (19) (Figure 6), that may be followed by widespread dissemination of small psoriasis-like lesions. Frequently, it is misdiagnosed

as a diaper dermatitis, and the suspicion of psoriasis only raises after multiple unresponsive treatments to the first condition (29).

- Congenital psoriasis is a very rare condition where plaque and erythrodermic types are the most common presentations. The implied mechanism may be Koebner Phenomenon in an already susceptible individual (20). Most of the times, congenital psoriasis is misdiagnosed as a more common entity, like seborrheic or atopic dermatitis. Adding to this, it is also possible that the child is already born with any of the later described conditions and only after some time develops true psoriasis. The most frequently involved areas of skin are the same as the ones in common childhood psoriasis, except for the diaper area, something that can be explained by the new-borns being diaper-naïve (62).
- Naevoid Blaschkoid consists of multiple psoriasiform plaques arranged along the lines of Blaschko, reflecting a possible mosaicism of a gene responsible for psoriasis (63). The pattern is not linear, but rather V-shaped on the back, S-shaped on the lateral and anterior parts of the trunk, whorl-shaped on the abdomen and with perpendicular lines on the limbs (63). Although it has a very peculiar and completely different location, clinical and histological aspects of the disease are the same as in common psoriasis.

Figure 1 – Onychodystrophy

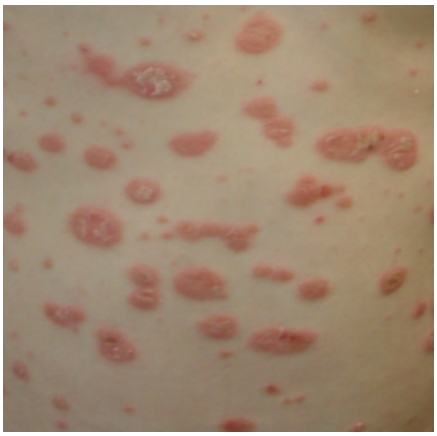

Figure 2 - Red-to-salmon coloured, small, oval plaques (guttate psoriasis)

Figures 3 and 4 – Guttate Psoriasis

Figure 5 – Inverse Psoriasis

Figure 6 – Diaper Psoriasis

Figure 7 – Allergic contact dermatitis caused by methylisothiazolinone

Diagnosis

Psoriasis diagnosis is usually made by clinical and physical examination findings. Special attention should be given to family history and potential trigger factors, such as recent infections, medications and trauma (2). Full inspection of the skin, nails and mucosa is imperative. In addition to this, direct examination and culture of nails specimens should be taken in suspicion of secondary bacterial and fungal infections (1). Typically found diagnostic features of psoriasis include the occurrence of Koebner Phenomenon, the Auspitz sign (arising of pinpoint bleeding after scale removal), remaining of residual pigmentation following lesion resolution and nail pitting (2, 5).

Weight, height and Body Mass Index should be assessed in all children with psoriasis, adding the evaluation of fasting lipid profile, fasting blood sugar and blood pressure to those at risk for metabolic syndrome. Laboratory investigations have a limited role on the diagnosis, although a complete blood count, ionogram and renal and hepatic function tests, should be considered in patients with severe generalized pustular psoriasis, since the results may be abnormal. When there is a suspicion of a streptococcal infection, especially in guttate type cases, a swab of the likely involved site (usually throat or perianal area) should be taken for culture (29).

Severity assessment (as well as treatment efficacy) is made by Psoriasis Area and Severity Index (PASI), which is considered the gold standard, being frequently used in clinical trials. It consists of four parameters assigned by an evaluator: erythema, thickness, scaliness and affected area in each of the four body sections (head and neck, trunk, upper limbs and lower limbs) (64), resulting in a score with values between 0 and 72. Despite this, PASI has significant limitations, since it is difficult to apply and also to interpret, and so is therefore not that meaningful for most physicians (65). Recently, some studies demonstrated that the product between Physician Global Assessment (PGA) and affected Body Surface Area (BSA) would give an alternative for PASI, with the advantage of being easier. PGA measures the qualities (degree of erythema, thickness and scaliness) of the plaques averaged over the entire body, resulting in values ranging from 0 to 5, where 0 is clear and 5 is severe. The affected BSA is defined as the percentage of the affected body area, where 1% corresponds to palm, fingers and thumb area of each patient (66).

Moreover, the presence of comorbidities and impact on quality of life must also account for severity measurement (29). Considering this, screening for metabolic, cardiovascular and mental health diseases is mandatory in severe psoriasis cases (67).

Skin biopsy is rarely used, mainly in children, being withheld, most of the times, only for doubtful cases. When its execution is necessary, any topical therapy should be previously discontinued, therefore any alteration on the samples will be prevented (68). Histological findings include: parakeratosis; hyperkeratosis; epidermal acanthosis, absence or reduction of the granular cell layer; elongation of the *rete ridges*; edema of the papillary dermis with dilated blood vessels; perivascular lymphocytic inflammatory infiltrates; and neutrophilic aggregates within the dermis and epidermis, also known as Munro microabcesses or pustules of Kogoj (2, 69). These characteristics may differ depending on the site of biopsy, psoriasis subtype and previous treatments taken by the patient (10). Recently, dermoscopy was suggested to help distinguishing psoriasis from other common skin conditions, like dermatitis, since distinctive findings on psoriatic plaques can be found (70).

Differential Diagnosis

In some cases of psoriasis, correct diagnosis can be a true challenge. Several skin conditions of inflammatory and/or infectious origin should be taken in account as differential diagnosis, depending on the disease type and location (29).

Eczema from variable causes, such as atopic, allergic contact, nummular or dyshidrotic is one of the most common differential diagnoses of all types of psoriasis (2, 29), as it can be seen on Table 1.

Recently, methylchloroisothiazolinone and methylisothiazolinone, present in many sanitizing hand and diaper wipes, have been reported to cause psoriasiform allergic contact dermatitis in periorificial or perineal area (Figure 7), and clinicians should ask about the use of these wipes (71, 72).

As regards inflammatory causes, seborrheic dermatitis must be considered mainly as a differential diagnosis of inverse or scalp psoriasis (1, 29). Other conditions include *pityriasis rosea*, an usually self-limited disease resolving in few weeks, characterized by round or oval papules or plaques, which may resemble guttate psoriasis, but can be distinguished from it especially by its large, single scaly plaque preceding the generalized lesions (1, 73); *pityriasis rubra pilaris*, which should be differentiated from erythrodermic type (73); and lichen planus (1, 2, 29).

Candidiasis and bacterial intertrigo, especially when there is body folds involvement; staphylococcal scalded skin syndrome, as an erythrodermic cause; secondary syphilis, mainly in guttate psoriasis cases; *tinea corporis* and *tinea capitis*; erythrasma; and onychomycosis make part of a list of infectious skin conditions that should be thought about within the possible differential diagnosis (1, 2, 29).

Table 1 – Differential Diagnosis of Pediatric Psoriasis

Types of Psoriasis	**Differential Diagnosis**
Plaque	Atopic dermatitis Nummular dermatitis Id reaction Pityriasis rubra pilaris Lichen planopilaris Tinea corporis
Scalp	Atopic dermatitis Seborrheic dermatitis Tinea capitis
Nail	Onychomycosis Lichen Planus
Guttate	Nummular dermatitis Id reaction Pityriasis rosea Pityriasis rubra pilaris Lichen planus Tinea corporis Secondary syphilis
Inverse	Allergic contact dermatitis Tinea corporis Erythrasma Candidiasis Bacterial intertrigo
Erythrodermic	Erythroderma by other causes: atopic dermatitis, pityriasis rubra pilaris, lichen planus, mycosis fungoides, staphylococcal scalded skin syndrome
Pustular	Infected contact or dyshidrotic dermatitis Tinea corporis Sweet syndrome Staphylococcal scalded syndrome (generalized pustular) Acute generalized exanthematous pustulosis (generalized pusutular)
Diaper	Allergic contact dermatitis Candidiasis Erythrasma

Comorbidities and Quality of Life Impact

As a systemic inflammatory condition, psoriasis is associated with considerable comorbidities, which have been the focus of several studies during the past years. Many of the ones recognized in adults are now proved to also affect pediatric patients (2).

Cardiovascular diseases and metabolic syndrome are two important entities that contribute substantially to morbidity in patients. Although not yet formally proven (74), the concept of *psoriatic march* has been proposed to explain the relationship between them and psoriasis (9, 67): systemic inflammation in psoriasis may cause insulin resistance, which triggers endothelial cell dysfunction, leading to atherosclerosis and, lastly, myocardial infarction and stroke. What it is known for sure is that psoriatic patients, especially the ones with severe disease, have raised cardiovascular risk factors (74). Augustin *et al* (2010) reported that hyperlipidemia, diabetes mellitus, hypertension and obesity, already known to be associated with adult patients, were also noted in children with psoriasis, with a two-fold increase compared to healthy subjects (6). This notwithstanding, a cross sectional, multicenter study in France, showed that childhood onset of psoriasis is not associated with the frequency of cardiovascular and metabolic comorbidities in adulthood (75).

Psoriasis might be an independent risk factor for metabolic syndrome. A small study made by Au S.C. *et al* (2012) demonstrated a higher prevalence of metabolic syndrome in children with psoriasis than in healthy controls (30% vs. 7.4% respectively), but statistically significant differences in Body Mass Index were not found in those two populations (22.7 vs. 22.3 for cases and controls respectively) (76). This may explain why even when there is control for weight and Body Mass Index, these children still have a tendency for higher blood lipids and metabolic syndrome (48, 76).

Excess adiposity and central distribution are more common in psoriatic children than in general population (77). Obesity may be a trigger for psoriasis (18, 19), since it is associated with a low-grade systemic inflammatory state, due to adipokines released by the interaction between adipocytes and macrophages (1). Koebnick *et al* (2011) showed that overweight, moderately obese and extremely obese children had a 1.31; 1.39 and 1.78, respectively, greater chance of having psoriasis, when compared to subjects with normal weight (48). This study and several others demonstrated that the

odds of obesity are even higher in children than in adults with psoriasis (50, 77-79). Obesity is also related with greater disease activity (5) and severity (75, 77).

Pediatric psoriasis may be linked to various autoimmune conditions and vice-versa (80). Rheumatoid Arthritis and Crohn's Disease are two and four times more prevalent in children with psoriasis, respectively (6); but the most recognized autoimmune comorbidity is, certainly, Psoriatic Arthritis (29). Its prevalence in children already affected with psoriasis ranges from 1 to 10% (52) and it is believed that it develops about one decade after skin disease onset (81). It presents as an oligoarthritis involving preferentially small joints, such as interphalangeal of the hands and feet, but over time, poliarthritis may develop, affecting larger joints (1, 82). Dactylitis is also a common feature (29).

Finally, just as important as the previous comorbidities, is the impact of psoriasis on psychological well-being and quality of life. In fact, the skin and brain influence each other, due to their common origin from the ectoderm (83). Juvenile psoriasis has a negative physical, emotional and social impact on children (84).

A comparative study between skin diseases and other chronic childhood diseases revealed that the former might have a quality of life impairment as high as diabetes mellitus, asthma or epilepsy. Together with atopic dermatitis, psoriasis was the skin disease with the most negative impact. Since they are visible to the others, skin conditions make the patient more prone to name calling and bullying (85). In another study, up to 65% of the children experienced feelings of stigmatization (84).

A study made by Kimball *et al* (2012) showed that pediatric patients had an 18 to 28% greater risk of being diagnosed with depression, anxiety or any other psychiatric disorder, compared to disease-free subjects. These children also have a 43% greater risk of taking psychotropic medication (86). These disorders may be due to pain, itching and visibility of the lesions (87, 88).

Parents may be psychologically affected by their child's disease as well. A correlation was found between the extent of the disease on a child and depression and anxiety in his parents or caregivers (89). Thus, the physician should assess not only the patient psychological status and quality of life impact, but also their family's, and try to educate all of them together (90).

Treatment

Most of the treatments approved for psoriasis in adults are the same that are used in children. Despite this, the majority of them are not yet approved, requiring off-label prescription (91). Efficacy and safety studies are lacking in this population, especially the ones with long-term follow-up and outcomes.

A considerable number of aspects should be taken into account when making decisions about a particular therapeutic regimen, including: age of the patient; severity of the disease and its impact on quality of life; lesions' morphology and involvement areas; cost and complexity of the treatment, as well as its practicability, tolerability and safety; and, finally, patient's preferences (41).

Since most of the children have mild-to-moderate disease, topical treatment is the most widely used, saving phototherapy and systemic therapy for severe or refractory cases, or those with psoriatic arthritis (41) or reduced quality of life (85).

Topical Therapies

Topical treatments are available in many different vehicles: creams, ointments, foams, gels, lotions, liquid solutions, sprays, oils, and drug impregnated tapes (92). The choice should be guided by the site and morphology of the lesions and patients' preferences. Thicker vehicles, such as ointments, are more occlusive and are rather used on the extremities. Creams can also be used at these sites. On the other hand, liquids, gels, lotions, sprays, oils or foams are preferred, for example, on the scalp. Additionally, oils and ointments should be reserved for night time use, since they are not as cosmetically acceptable as the other options (92).

First-line topical therapy for all types of psoriasis includes corticosteroids, vitamin D_3 analogues, calcineurin inhibitors and keratolytics, as adjuvants.

The most commonly used agents are corticosteroids, which work by their anti-inflammatory, anti-pruritic and anti-proliferative properties, reducing erythema, scaling and pruritus (41). They are available in a wide variety of vehicles and potencies: more sensitive sites, like intertriginous areas, head and neck are treated with lower potencies (Class V-VII); whereas in scalp, trunk and extremities (including palms and soles), higher potencies agents (Class II-IV) are more indicated (92, 93). Class I corticosteroids should be reserved only for short-term therapy (less than two weeks) of thick, refractory lesions (94). Together with other high-potency agents, they can cause striae,

telangiectasias and atrophy of the skin as well as hypothalamic-pituitary-adrenal axis suppression with continued usage (29, 94). Special attention must be given to the proximal medial aspect of the extremities, because of its high tendency for developing striae and atrophy with high-potency corticosteroids usage (92). Extremely potent agents may also be avoided or carefully used in infants (92), mainly because they have a high ratio of body surface area to mass, which can result in systemic absorption (95). With the propose to decrease the risk of adverse effects, corticosteroids are occasionally combined or rotated with other non-steroidal agents, for instance vitamin D_3 analogues (92).

Calcipotriol and calcitriol are two vitamin D_3 analogues that act by inhibiting keratinocyte proliferation and inducing its differentiation (96). They can be used as monotherapy or, as previously stated, along with corticosteroids, once they appear to have synergistic effects (41). Aside from their documented efficacy and safety in children (92), these agents also have relatively low risk of adverse effects (41). The most common are localized skin irritation and pruritus (10), whereby they should be used carefully in thinner skin areas (68). Systemic absorption is also an aspect that must be taken into account in patients with prolonged therapy or significant areas involved, as it can provoke changes in seric calcium and, consequently, in phosphate and vitamin D levels (10, 94). A study made by Darley *et al* (1996) concluded that total weekly doses of $45g/m^2$ are effective in children, without modifying calcium homeostasis (97).

In order to facilitate the usage and enhance patient's compliance, there is available a compounded formulation containing both calcipotriol and betamethasone dipropionate. Its efficacy and safety in pediatric population was described in three different studies (98-100).

Topical calcineurin inhibitors, tacrolimus and pimecrolimus, are non-steroidal immunomodulators approved for atopic dermatitis treatment, that are frequently used off-label for psoriasis treatment in children (101). They are effective and safe, especially on the treatment of sensitive areas, like face and intertriginous sites, frequently prone to develop adverse effects when on long-term therapy with topical corticosteroids (102, 103). Their efficacy on thick plaque psoriasis on elbows, knees and trunk has not been proved yet (92). Their mechanism of action consists on the blockade of calcineurin enzyme, inhibiting IL-2 production and consequent T-lymphocytes activation and proliferation (104). The most regularly reported side effects are burning and pruritus, mainly if they are applied on fissured plaques (92). Apart from that, their

combination with UV light must be avoided based on the risk of developing skin cancer and lymphoma (10).

Keratolytics are frequently used as adjuvants in topical treatment. Salicylic acid and urea are the most common and they work by removing superficial hyperkeratosis, allowing secondary penetration of topical medications (94). They also make skin less agreeable by trauma, which could trigger Koebner Phenomenon (105). There are no published studies on the specific use of these agents in children (41). The use of salicylic acid in children under 2 years is not recommended due to the increased risk of systemic absorption and consequent salicylism. Ideally, it should only be prescribed for children older than 6 years of age (105).

Currently, tazarotene, anthralin and coal tar are used as second-line topical therapies. Tazarotene, a topical retinoid, reduces keratinocyte proliferation and promotes differentiation, and it is typically used in association with topical corticosteroids (41). Its efficacy and safety are not documented in children, but it is approved for adult psoriasis treatment. Local skin irritation is the most common side effect (29). Successful use to treat nail psoriasis in children has been reported (106). Anthralin has anti-inflammatory and anti-proliferative proprieties and is effective and safe for pediatric use (10). It should be prescribed as short-contact therapy in order to avoid skin irritation and staining (29). Coal tar, a keratolytic and anti-inflammatory compound, is mostly indicated for thick psoriasis on the trunk, extremities and scalp (107). Although it is generally well-tolerated it can stain clothes (108) and cause local irritation, folliculitis and photosensitivity (29). Concentrations greater than 5% should be avoided owing the increased risk of carcinogenesis (41).

Phototherapy

Phototherapy, an effective and safe treatment for children, is mainly used in cases of plaque or guttate psoriasis, which are refractory to topical therapy; diffuse involvement of the body (more than 15-20% of the body surface area); debilitating palmo-plantar disease; and patients who cannot receive systemic treatment (10, 109). It should be used in children old enough to stand still in a phototherapy booth (94). Moreover it requires patience and time commitment from both the child and his family, since the treatments should be performed two or three times per week (110, 111).

Phototherapy works by inhibiting DNA synthesis and keratinocyte proliferation, as well as inducing apoptosis of T-lymphocytes and anti-inflammatory mediators production (112). Three types of UV light are used: broad-band UVB (290-320nm), narrow-band UVB (311-313nm) and UVA (320-400nm) (113). The most widely used in children is narrow-band UVB (NB-UVB), since it shows good results and has milder side effects compared to the others (114). It is especially effective on guttate and thin plaque disease (115, 116), in all skin types (117-120). Patient age, duration and extent of the disease have little relationship to cumulative clearance dose, number of sittings and therapy duration (117). Short-term side effects include xerosis, itch, erythema, blistering and herpes virus reactivation (119). Photoaging and increased risk of carcinogenesis are also possible long-term side effects, but specific data in children is lacking (121). NB-UVB can be combined with topical vitamin D_3 analogues (122), tazaroten (123) and anthralin (124), enhancing its efficacy while reducing radiation side effects. Preliminary use of emollients also seems to increase phototherapy efficacy (125).

UVA phototherapy with photosensitizing psoralen – PUVA is another alternative for children, although no solid conclusions exist on its efficacy and safety (114), since only a small number of patients was treated with it (116). Oral psoralen must be taken 90 minutes before each UVA exposure (113) and it is not recommended for children younger than 12 years because of its toxicity related to ingestion. Side effects include nausea and vomiting, headache, keratitis, hepatic toxicity and generalized photosensization, which requires photoprotection for 24 hours (126, 127). The main long-term side effects are cataracts, photoaging and increased risk of skin cancer (126). Topical PUVA is a safer alternative, but long-term carcinogenicity data in children is missing (128).

Systemic Therapies

There are no formalized treatment or monitoring guidelines regarding systemic therapy on pediatric psoriasis (92), and only limited data exits on the safety and efficacy of these medications usage (41). The most commonly used are retinoids (acitretin), methotrexate and cyclosporine, based on collected knowledge of their benefits and risks in children with other conditions, like ichthyosis, juvenile rheumatoid arthritis and organ transplantation, respectively (92). These agents can also be combined with topical

drugs or phototherapy (41), or used in sequential or rotation strategy in order to maximize their benefits and decrease adverse effects (113).

Methotrexate can be considered the systemic therapy of choice in treatment of severe or refractory plaque, pustular or erythrodermic psoriasis or when psoriatic arthritis co-exists (41, 113, 114). It has anti-inflammatory and immunosuppressive effects, inhibiting the production of inflammatory cytokines by T-cell lymphocytes by RNA and DNA synthesis blockage and cycle cell arrest (41). There is no consensus about methotrexate dose regimen and treatment in pediatric patients (10). Dose escalations can be done until the therapeutic control is achieved and then tapered to maintenance dose, in order to reduce side effects (129). Efficacy can be obtained with doses between 0.2 and 0.7 mg/kg per week (130). Studies on polyglutamate assay showed an efficacy of this method in identifying patients needing dose escalation (131). This assay consists on measuring the concentration of methotrexate predominant metabolite, triglutamate, in red blood cells by high performance liquid chromatography by fluorescent analysis (132). Higher numbers on this assay are associated with better response to the therapy (131). Methotrexate is associated with short and long-term side effects. Pancytopenia, pulmonary and hepatic toxicity, renal insufficiency and osteopathy are the most dangerous ones (41). Despite this, they are less frequent in children than in adults, maybe due to the lower comorbidities and usage of concomitant medication in this age (101). Methotrexate interacts with numerous drugs, including nonsteroidal anti-inflammatories (133, 134) and trimethoprim-sulfamethoxazole (135).

Acitretin, a second-generation retinoid, works by binding to nuclear receptors in keratinocytes, promoting differentiation and inhibiting their proliferation, reducing inflammation at the same time (41). It is used mainly in maintenance therapy in cases of severe plaque or guttate, pustular and erythrodermic psoriasis and in intermittent rescue therapy of generalized erythrodermic psoriasis cases (113, 136). Acitretin doses should be kept between 0.5 and 1 mg/kg per day or below, in order to avoid toxicities (113). The most referred ones are xerosis, cheilitis, skin fragility, blepharo-conjunctivitis, cataracts, myalgias, arthralgias, transient liver transaminases and triglycerids elevation, and bone alterations (premature epiphyseal closure, osteoporosis and hyperostosis) (1, 41, 94). Regarding this, monitoring of blood cell counts, liver enzymes and lipids must be done during the course of therapy (94). Since acitretin is a teratogenic drug, oral contraceptives should be initiated one month before the start and continued three years

after the end of therapy (94), since, in the presence of ethanol, acitretin is converted to etretinate that remains in the system for this period of time (113).

Cyclosporine, which is commonly used in children for the prevention and treatment of transplant rejection (113), has anti-inflammatory and immunosuppressive effects. It works by binding to a protein called cyclophilin, giving rise to a complex that is able to inhibit calcineurin, decreasing cytokines production and T-cell proliferation (41). In pediatric patients with psoriasis, it can be effective with doses ranging from 1.5 to 5 mg/kg per day for six months to one or two years (137-141), but not exceeding that because of its cumulative toxicity (114). It is mainly used in rapidly evolving and refractory plaque or pustular psoriasis (113), alone or in combination with topical agents or acitretin (137), but not with phototherapy because of an increased risk of squamous cell carcinoma development (41). Doses may be higher than the ones prescribed for adults because of differences in pharmacokinetics and the existence of a greater body surface area to weight ratio in children (113, 139, 140, 142). Clinical improvement starts to be observed in four to eight weeks and, once the disease is stable for two or three months, tapering of the dose should be done, adjusting it on the basis of clinical response, creatinine levels and blood pressure values (113). These last two parameters are included since cyclosporine can bear renal insufficiency and hypertension as side effects; so, close monitoring of renal function and blood pressure is mandatory. Other adverse effects include nausea and vomiting, hypertrichosis, gingival hyperplasia, headache, myalgias, electrolyte abnormalities, hyperuricemia and hyperlipidemia (41).

Biologic Therapies

Biologic agents constitute attractive therapies for psoriasis treatment. Most of them have also been recently approved for treatment in children. The most commonly used are Tumor Necrosis Factor-α inhibitors etarnecept, infliximab and adalimumab (92). Biologics are very convenient since they have better dose regimens and less requirement of laboratory monitoring, when compared to the other systemic therapies (10); because they work as targeted therapy, toxicity potential is much lower as well (113). However, serious complications in pediatric patients with juvenile inflammatory arthritis treated with these agents were reported, including occurrence of opportunistic infections, tuberculosis reactivation, malignancies, auto-antibodies and demyelinating diseases (143). Regarding this, biologics are considered second or third-line agents, restricted to severe and/or refractory cases of plaque, pustular and erythrodermic

psoriasis (113), or those with psoriatic arthritis co-existence (41). All patients should take a tuberculosis screening test and laboratory studies before initiating therapy (113).

Etarnecept has the most significant published data concerning its use in children (144, 145), in part because it is approved for the treatment of juvenile inflammatory arthritis in patients who are 2 years or older (113). In 2008, a double-blind multicenter, phase III, randomized controlled trial evaluated the safety and efficacy of this agent in 4 to 17 year old children with moderate to severe plaque psoriasis. It was well tolerated and demonstrated significant reduction on the severity of the disease. Pharangytis, bronchitis and gastroenteritis were the most common side effects during the trial (146). Based on its efficacy and safety profile, in 2009 the European Medicines Agency approved the use of etarnecept for the treatment of severe plaque psoriasis in children who are at least 8 years old, who turn up to be intolerant or inadequately controlled by other systemic therapies or phototherapy (147).

Infliximab and adalimumab are approved for the treatment of Crohn's disease in children who are 6 years or older and for moderate to severe polyarticular juvenile inflammatory arthritis in children who are 4 years or older, respectively (148, 149). Infliximab use in pediatric psoriasis is only limited to case reports and anecdotal experience (113). Interestingly, a Finnish prospective study of infliximab side effects in 84 children with inflammatory bowel disease showed that 47.6% of the participants developed chronic skin reactions, where psoriasiform lesions were the most common (150). Adalimumab is now approved for treatment of severe chronic plaque psoriasis in children older than 4 years who have a poor response to or are not candidates for topical therapies or phototherapy (149).

New biologic agents have been approved for the treatment of adult psoriasis, including ustekinumab, a monoclonal antibody against p40 subunit of IL-12 and IL-23 (151-153), which is now indicated for children older than 12 years with moderate to severe plaque psoriasis who are intolerant or inadequately controlled by other therapies (154). A phase III, multicenter, randomized, double-blind placebo-controlled trial taken in United States, about the efficacy and safety of ustekinumab in adolescents was recently completed, with 54.1% and 61.1% of the patients receiving half and standard dose, respectively, achieving a 90% improvement in PASI score at week 12, compared with 5.4% of the patients on placebo (155).

Conclusion

Psoriasis consists in much more than a disease confined to the skin. It is a chronic systemic inflammatory condition, associated with a wide variety of comorbidities that should not be missed by the physician. Frequent monitoring and assistance are mandatory. Educating the patient and his close family is essential, so the aim to provide the child a better quality of life can be achieved.

Although much is known already about psoriasis in pediatric patients, standardized guidelines on the management and treatment of the disease in this age group are lacking. Albeit a number of biologic agents have been lately approved for pediatric usage, some of the topical and the majority of systemic therapies are not approved yet. They are often prescribed off-label, based on their efficacy and safety in adults, since long-term data in children is missing. Regarding this, there is a great need for systematic evaluation of therapeutic agents amongst this population.

References

1. Matteo M, Maddalena N, Balato A, Scalvenzi M, Cirillo T, Gallo L, et al. Psoriasis in Children: A Review. Curr Pediatr Rev. 2015;11(1):10-26.
2. Boehncke WH, Schon MP. Psoriasis. Lancet. 2015;386(9997):983-94.
3. Henseler T, Christophers E. Psoriasis of early and late onset: characterization of two types of psoriasis vulgaris. J Am Acad Dermatol. 1985;13(3):450-6.
4. Tollefson MM, Crowson CS, McEvoy MT, Maradit Kremers H. Incidence of psoriasis in children: a population-based study. J Am Acad Dermatol. 2010;62(6):979-87.
5. Silverberg NB. Update on pediatric psoriasis. Cutis. 2015;95(3):147-52.
6. Augustin M, Glaeske G, Radtke MA, Christophers E, Reich K, Schafer I. Epidemiology and comorbidity of psoriasis in children. Br J Dermatol. 2010;162(3):633-6.
7. Parisi R, Symmons DP, Griffiths CE, Ashcroft DM, Identification, Management of P, et al. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol. 2013;133(2):377-85.
8. Chiam LY, de Jager ME, Giam YC, de Jong EM, van de Kerkhof PC, Seyger MM. Juvenile psoriasis in European and Asian children: similarities and differences. Br J Dermatol. 2011;164(5):1101-3.
9. Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. Lancet. 2007;370(9583):263-71.
10. Bronckers IM, Paller AS, van Geel MJ, van de Kerkhof PC, Seyger MM. Psoriasis in Children and Adolescents: Diagnosis, Management and Comorbidities. Paediatr Drugs. 2015;17(5):373-84.
11. Roberson ED, Bowcock AM. Psoriasis genetics: breaking the barrier. Trends Genet. 2010;26(9):415-23.
12. Farber EM, Nall ML. The natural history of psoriasis in 5,600 patients. Dermatologica. 1974;148(1):1-18.
13. Veal CD, Capon F, Allen MH, Heath EK, Evans JC, Jones A, et al. Family-based analysis using a dense single-nucleotide polymorphism-based map defines genetic variation at PSORS1, the major psoriasis-susceptibility locus. Am J Hum Genet. 2002;71(3):554-64.

14. Nair RP, Stuart PE, Nistor I, Hiremagalore R, Chia NV, Jenisch S, et al. Sequence and haplotype analysis supports HLA-C as the psoriasis susceptibility 1 gene. Am J Hum Genet. 2006;78(5):827-51.
15. Romiti R, Maragno L, Arnone M, Takahashi MD. [Psoriasis in childhood and adolescence]. An Bras Dermatol. 2009;84(1):9-20.
16. Gudjonsson JE, Karason A, Runarsdottir EH, Antonsdottir AA, Hauksson VB, Jonsson HH, et al. Distinct clinical differences between HLA-Cw*0602 positive and negative psoriasis patients--an analysis of 1019 HLA-C- and HLA-B-typed patients. J Invest Dermatol. 2006;126(4):740-5.
17. Asumalahti K, Ameen M, Suomela S, Hagforsen E, Michaelsson G, Evans J, et al. Genetic analysis of PSORS1 distinguishes guttate psoriasis and palmoplantar pustulosis. J Invest Dermatol. 2003;120(4):627-32.
18. Ferrandiz C, Pujol RM, Garcia-Patos V, Bordas X, Smandia JA. Psoriasis of early and late onset: a clinical and epidemiologic study from Spain. J Am Acad Dermatol. 2002;46(6):867-73.
19. Silverberg NB. Update on pediatric psoriasis, part 1: clinical features and demographics. Cutis. 2010;86(3):118-24.
20. Li Y, Begovich AB. Unraveling the genetics of complex diseases: susceptibility genes for rheumatoid arthritis and psoriasis. Semin Immunol. 2009;21(6):318-27.
21. Sugiura K. The genetic background of generalized pustular psoriasis: IL36RN mutations and CARD14 gain-of-function variants. J Dermatol Sci. 2014;74(3):187-92.
22. Marrakchi S, Guigue P, Renshaw BR, Puel A, Pei XY, Fraitag S, et al. Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. N Engl J Med. 2011;365(7):620-8.
23. Lee E, Trepicchio WL, Oestreicher JL, Pittman D, Wang F, Chamian F, et al. Increased expression of interleukin 23 p19 and p40 in lesional skin of patients with psoriasis vulgaris. J Exp Med. 2004;199(1):125-30.
24. Lowes MA, Chamian F, Abello MV, Fuentes-Duculan J, Lin SL, Nussbaum R, et al. Increase in TNF-alpha and inducible nitric oxide synthase-expressing dendritic cells in psoriasis and reduction with efalizumab (anti-CD11a). Proc Natl Acad Sci U S A. 2005;102(52):19057-62.

25. Nestle FO, Conrad C, Tun-Kyi A, Homey B, Gombert M, Boyman O, et al. Plasmacytoid predendritic cells initiate psoriasis through interferon-alpha production. J Exp Med. 2005;202(1):135-43.
26. Gilliet M, Lande R. Antimicrobial peptides and self-DNA in autoimmune skin inflammation. Curr Opin Immunol. 2008;20(4):401-7.
27. Locksley RM, Killeen N, Lenardo MJ. The TNF and TNF receptor superfamilies: integrating mammalian biology. Cell. 2001;104(4):487-501.
28. Parham C, Chirica M, Timans J, Vaisberg E, Travis M, Cheung J, et al. A receptor for the heterodimeric cytokine IL-23 is composed of IL-12Rbeta1 and a novel cytokine receptor subunit, IL-23R. J Immunol. 2002;168(11):5699-708.
29. Tollefson MM. Diagnosis and management of psoriasis in children. Pediatr Clin North Am. 2014;61(2):261-77.
30. Lowes MA, Bowcock AM, Krueger JG. Pathogenesis and therapy of psoriasis. Nature. 2007;445(7130):866-73.
31. Underwood MA, Bevins CL. Defensin-barbed innate immunity: clinical associations in the pediatric population. Pediatrics. 2010;125(6):1237-47.
32. Girolomoni G, Mrowietz U, Paul C. Psoriasis: rationale for targeting interleukin-17. Br J Dermatol. 2012;167(4):717-24.
33. Buchau AS, Gallo RL. Innate immunity and antimicrobial defense systems in psoriasis. Clin Dermatol. 2007;25(6):616-24.
34. Rosenberger C, Solovan C, Rosenberger AD, Jinping L, Treudler R, Frei U, et al. Upregulation of hypoxia-inducible factors in normal and psoriatic skin. J Invest Dermatol. 2007;127(10):2445-52.
35. Schon MP, Zollner TM, Boehncke WH. The molecular basis of lymphocyte recruitment to the skin: clues for pathogenesis and selective therapies of inflammatory disorders. J Invest Dermatol. 2003;121(5):951-62.
36. Camargo CM, Brotas AM, Ramos-e-Silva M, Carneiro S. Isomorphic phenomenon of Koebner: facts and controversies. Clin Dermatol. 2013;31(6):741-9.
37. Gupta MA, Gupta AK, Watteel GN. Cigarette smoking in men may be a risk factor for increased severity of psoriasis of the extremities. Br J Dermatol. 1996;135(5):859-60.

38. Ozden MG, Tekin NS, Gurer MA, Akdemir D, Dogramaci C, Utas S, et al. Environmental risk factors in pediatric psoriasis: a multicenter case-control study. Pediatr Dermatol. 2011;28(3):306-12.
39. Busch AL, Landau JM, Moody MN, Goldberg LH. Pediatric psoriasis. Skin Therapy Lett. 2012;17(1):5-7.
40. Basavaraj KH, Ashok NM, Rashmi R, Praveen TK. The role of drugs in the induction and/or exacerbation of psoriasis. Int J Dermatol. 2010;49(12):1351-61.
41. Shah KN. Diagnosis and treatment of pediatric psoriasis: current and future. Am J Clin Dermatol. 2013;14(3):195-213.
42. Gudjonsson JE, Thorarinsson AM, Sigurgeirsson B, Kristinsson KG, Valdimarsson H. Streptococcal throat infections and exacerbation of chronic plaque psoriasis: a prospective study. Br J Dermatol. 2003;149(3):530-4.
43. Perez-Lorenzo R, Zambrano-Zaragoza JF, Saul A, Jimenez-Zamudio L, Reyes-Maldonado E, Garcia-Latorre E. Autoantibodies to autologous skin in guttate and plaque forms of psoriasis and cross-reaction of skin antigens with streptococcal antigens. Int J Dermatol. 1998;37(7):524-31.
44. Besgen P, Trommler P, Vollmer S, Prinz JC. Ezrin, maspin, peroxiredoxin 2, and heat shock protein 27: potential targets of a streptococcal-induced autoimmune response in psoriasis. J Immunol. 2010;184(9):5392-402.
45. Santamaria-Babi LF. CLA(+) T cells in cutaneous diseases. Eur J Dermatol. 2004;14(1):13-8.
46. Ferran M, Galvan AB, Rincon C, Romeu ER, Sacrista M, Barboza E, et al. Streptococcus induces circulating CLA(+) memory T-cell-dependent epidermal cell activation in psoriasis. J Invest Dermatol. 2013;133(4):999-1007.
47. Nograles KE, Zaba LC, Shemer A, Fuentes-Duculan J, Cardinale I, Kikuchi T, et al. IL-22-producing "T22" T cells account for upregulated IL-22 in atopic dermatitis despite reduced IL-17-producing TH17 T cells. J Allergy Clin Immunol. 2009;123(6):1244-52 e2.
48. Koebnick C, Black MH, Smith N, Der-Sarkissian JK, Porter AH, Jacobsen SJ, et al. The association of psoriasis and elevated blood lipids in overweight and obese children. J Pediatr. 2011;159(4):577-83.

49. Bryld LE, Sorensen TI, Andersen KK, Jemec GB, Baker JL. High body mass index in adolescent girls precedes psoriasis hospitalization. Acta Derm Venereol. 2010;90(5):488-93.
50. Becker L, Tom WL, Eshagh K, Benjamin LT, Paller AS. Excess adiposity preceding pediatric psoriasis. JAMA Dermatol. 2014;150(5):573-4.
51. Howard R, Tsuchiya A. Adult skin disease in the pediatric patient. Dermatol Clin. 1998;16(3):593-608.
52. Mercy K, Kwasny M, Cordoro KM, Menter A, Tom WL, Korman N, et al. Clinical manifestations of pediatric psoriasis: results of a multicenter study in the United States. Pediatr Dermatol. 2013;30(4):424-8.
53. Reich K. Approach to managing patients with nail psoriasis. J Eur Acad Dermatol Venereol. 2009;23 Suppl 1:15-21.
54. Langenbruch A, Radtke MA, Krensel M, Jacobi A, Reich K, Augustin M. Nail involvement as a predictor of concomitant psoriatic arthritis in patients with psoriasis. Br J Dermatol. 2014;171(5):1123-8.
55. Tan AL, Benjamin M, Toumi H, Grainger AJ, Tanner SF, Emery P, et al. The relationship between the extensor tendon enthesis and the nail in distal interphalangeal joint disease in psoriatic arthritis--a high-resolution MRI and histological study. Rheumatology (Oxford). 2007;46(2):253-6.
56. Raposo I, Torres T. Nail psoriasis as a predictor of the development of psoriatic arthritis. Actas Dermosifiliogr. 2015;106(6):452-7.
57. Wilson FC, Icen M, Crowson CS, McEvoy MT, Gabriel SE, Kremers HM. Incidence and clinical predictors of psoriatic arthritis in patients with psoriasis: a population-based study. Arthritis Rheum. 2009;61(2):233-9.
58. Martin BA, Chalmers RJ, Telfer NR. How great is the risk of further psoriasis following a single episode of acute guttate psoriasis? Arch Dermatol. 1996;132(6):717-8.
59. Honig PJ. Guttate psoriasis associated with perianal streptococcal disease. J Pediatr. 1988;113(6):1037-9.
60. Popadic S, Nikolic M. Pustular psoriasis in childhood and adolescence: a 20-year single-center experience. Pediatr Dermatol. 2014;31(5):575-9.
61. Liao PB, Rubinson R, Howard R, Sanchez G, Frieden IJ. Annular pustular psoriasis--most common form of pustular psoriasis in children: report of three cases and review of the literature. Pediatr Dermatol. 2002;19(1):19-25.

62. Lehman JS, Rahil AK. Congenital psoriasis: case report and literature review. Pediatr Dermatol. 2008;25(3):332-8.
63. Ghorpade AK. Naevoid Blaschkoid psoriasis. Indian J Dermatol Venereol Leprol. 2010;76(4):449.
64. Hani AF, Prakasa E, Nugroho H, Affandi AM, Hussein SH. Body surface area measurement and soft clustering for PASI area assessment. Conf Proc IEEE Eng Med Biol Soc. 2012;2012:4398-401.
65. Walsh JA, McFadden M, Woodcock J, Clegg DO, Helliwell P, Dommasch E, et al. Product of the Physician Global Assessment and body surface area: a simple static measure of psoriasis severity in a longitudinal cohort. J Am Acad Dermatol. 2013;69(6):931-7.
66. Finlay AY. Avoiding palmar ambiguity in the PREPI: a handprint is approximately 1% body surface area. Br J Dermatol. 2011;164(3):679; author reply 80.
67. Boehncke WH, Boehncke S, Schon MP. Managing comorbid disease in patients with psoriasis. BMJ. 2010;340:b5666.
68. Stahle M, Atakan N, Boehncke WH, Chimenti S, Dauden E, Giannetti A, et al. Juvenile psoriasis and its clinical management: a European expert group consensus. J Dtsch Dermatol Ges. 2010;8(10):812-8.
69. Murphy M, Kerr P, Grant-Kels JM. The histopathologic spectrum of psoriasis. Clin Dermatol. 2007;25(6):524-8.
70. Lallas A, Kyrgidis A, Tzellos TG, Apalla Z, Karakyriou E, Karatolias A, et al. Accuracy of dermoscopic criteria for the diagnosis of psoriasis, dermatitis, lichen planus and pityriasis rosea. Br J Dermatol. 2012;166(6):1198-205.
71. Gul Mert G, Incecik F, Gunasti S, Herguner O, Altunbasak S. Psoriasiform drug eruption associated with sodium valproate. Case Rep Pediatr. 2013;2013:823469.
72. Chang MW, Nakrani R. Six children with allergic contact dermatitis to methylisothiazolinone in wet wipes (baby wipes). Pediatrics. 2014;133(2):e434-8.
73. Balato N, Di Costanzo L, Balato A. Differential diagnosis of psoriasis. J Rheumatol Suppl. 2009;83:24-5.

74. Boehncke WH, Boehncke S, Tobin AM, Kirby B. The 'psoriatic march': a concept of how severe psoriasis may drive cardiovascular comorbidity. Exp Dermatol. 2011;20(4):303-7.
75. Mahe E, Maccari F, Beauchet A, Lahfa M, Barthelemy H, Reguiai Z, et al. Childhood-onset psoriasis: association with future cardiovascular and metabolic comorbidities. Br J Dermatol. 2013;169(4):889-95.
76. Au SC, Goldminz AM, Loo DS, Dumont N, Levine D, Volf E, et al. Association between pediatric psoriasis and the metabolic syndrome. J Am Acad Dermatol. 2012;66(6):1012-3.
77. Paller AS, Mercy K, Kwasny MJ, Choon SE, Cordoro KM, Girolomoni G, et al. Association of pediatric psoriasis severity with excess and central adiposity: an international cross-sectional study. JAMA Dermatol. 2013;149(2):166-76.
78. Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB, Gelfand JM. Prevalence of cardiovascular risk factors in patients with psoriasis. J Am Acad Dermatol. 2006;55(5):829-35.
79. Love TJ, Qureshi AA, Karlson EW, Gelfand JM, Choi HK. Prevalence of the metabolic syndrome in psoriasis: results from the National Health and Nutrition Examination Survey, 2003-2006. Arch Dermatol. 2011;147(4):419-24.
80. Prahalad S, McCracken CE, Ponder LA, Angeles-Han ST, Rouster Stevens KA, Vogler LB, et al. Familial autoimmunity in the childhood arthritis and rheumatology research alliance registry. Pediatr Rheumatol Online J. 2016;14(1):14.
81. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis. 2005;64 Suppl 2:ii14-7.
82. Burgos-Vargas R. Juvenile onset spondyloarthropathies: therapeutic aspects. Ann Rheum Dis. 2002;61 Suppl 3:iii33-9.
83. Mercan S, Kivanc Altunay I. [Psychodermatology: a collaboration between psychiatry and dermatology]. Turk Psikiyatri Derg. 2006;17(4):305-13.
84. de Jager ME, De Jong EM, Evers AW, Van De Kerkhof PC, Seyger MM. The burden of childhood psoriasis. Pediatr Dermatol. 2011;28(6):736-7.
85. Beattie PE, Lewis-Jones MS. A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. Br J Dermatol. 2006;155(1):145-51.

86. Kimball AB, Wu EQ, Guerin A, Yu AP, Tsaneva M, Gupta SR, et al. Risks of developing psychiatric disorders in pediatric patients with psoriasis. J Am Acad Dermatol. 2012;67(4):651-7 e1-2.
87. Akay A, Pekcanlar A, Bozdag KE, Altintas L, Karaman A. Assessment of depression in subjects with psoriasis vulgaris and lichen planus. J Eur Acad Dermatol Venereol. 2002;16(4):347-52.
88. Russo PA, Ilchef R, Cooper AJ. Psychiatric morbidity in psoriasis: a review. Australas J Dermatol. 2004;45(3):155-9; quiz 60-1.
89. Manzoni AP, Weber MB, Nagatomi AR, Pereira RL, Townsend RZ, Cestari TF. Assessing depression and anxiety in the caregivers of pediatric patients with chronic skin disorders. An Bras Dermatol. 2013;88(6):894-9.
90. Lin VW. Tough-skinned kids: identifying psychosocial effects of psoriasis and helping pediatric patients and families cope. J Pediatr Nurs. 2012;27(5):563-72.
91. Sticherling M, Augustin M, Boehncke WH, Christophers E, Domm S, Gollnick H, et al. Therapy of psoriasis in childhood and adolescence - a German expert consensus. J Dtsch Dermatol Ges. 2011;9(10):815-23.
92. Bhutani T, Kamangar F, Cordoro KM. Management of pediatric psoriasis. Pediatr Ann. 2012;41(1):e1-7.
93. Kiken DA, Silverberg NB. Atopic dermatitis in children, part 2: treatment options. Cutis. 2006;78(6):401-6.
94. Silverberg NB. Update on pediatric psoriasis, Part 2: Therapeutic management. Cutis. 2010;86(4):172-6.
95. Cornell RC, Stoughton RB. Correlation of the vasoconstriction assay and clinical activity in psoriasis. Arch Dermatol. 1985;121(1):63-7.
96. O'Neill JL, Feldman SR. Vitamine D analogue-based therapies for psoriasis. Drugs Today (Barc). 2010;46(5):351-60.
97. Darley CR, Cunliffe WJ, Green CM, Hutchinson PE, Klaber MR, Downes N. Safety and efficacy of calcipotriol ointment (Dovonex) in treating children with psoriasis vulgaris. Br J Dermatol. 1996;135(3):390-3.
98. van Geel MJ, Mul K, Oostveen AM, van de Kerkhof PC, de Jong EM, Seyger MM. Calcipotriol/betamethasone dipropionate ointment in mild-to-moderate paediatric psoriasis: long-term daily clinical practice data in a prospective cohort. Br J Dermatol. 2014;171(2):363-9.

99. Oostveen AM, de Jong EM, Donders AR, van de Kerkhof PC, Seyger MM. Treatment of paediatric scalp psoriasis with calcipotriene/betamethasone dipropionate scalp formulation: effectiveness, safety and influence on children's quality of life in daily practice. J Eur Acad Dermatol Venereol. 2015;29(6):1193-7.
100. Gooderham M, Debarre JM, Keddy-Grant J, Xu Z, Kurvits M, Goodfield M. Safety and efficacy of calcipotriol plus betamethasone dipropionate gel in the treatment of scalp psoriasis in adolescents 12-17 years of age. Br J Dermatol. 2014;171(6):1470-7.
101. Cordoro KM. Topical therapy for the management of childhood psoriasis: part I. Skin Therapy Lett. 2008;13(3):1-3.
102. Brune A, Miller DW, Lin P, Cotrim-Russi D, Paller AS. Tacrolimus ointment is effective for psoriasis on the face and intertriginous areas in pediatric patients. Pediatr Dermatol. 2007;24(1):76-80.
103. Steele JA, Choi C, Kwong PC. Topical tacrolimus in the treatment of inverse psoriasis in children. J Am Acad Dermatol. 2005;53(4):713-6.
104. Nghiem P, Pearson G, Langley RG. Tacrolimus and pimecrolimus: from clever prokaryotes to inhibiting calcineurin and treating atopic dermatitis. J Am Acad Dermatol. 2002;46(2):228-41.
105. Fluhr JW, Cavallotti C, Berardesca E. Emollients, moisturizers, and keratolytic agents in psoriasis. Clin Dermatol. 2008;26(4):380-6.
106. Diluvio L, Campione E, Paterno EJ, Mordenti C, El Hachem M, Chimenti S. Childhood nail psoriasis: a useful treatment with tazarotene 0.05%. Pediatr Dermatol. 2007;24(3):332-3.
107. Cram DL. Psoriasis: treatment with a tar gel. Cutis. 1976;17(6):1197-8, 202-3.
108. Paghdal KV, Schwartz RA. Topical tar: back to the future. J Am Acad Dermatol. 2009;61(2):294-302.
109. Cordoro KM. Systemic and light therapies for the management of childhood psoriasis: part II. Skin Therapy Lett. 2008;13(4):1-3.
110. Dawe RS, Wainwright NJ, Cameron H, Ferguson J. Narrow-band (TL-01) ultraviolet B phototherapy for chronic plaque psoriasis: three times or five times weekly treatment? Br J Dermatol. 1998;138(5):833-9.
111. Leenutaphong V, Nimkulrat P, Sudtim S. Comparison of phototherapy two times and four times a week with low doses of narrow-band ultraviolet B in

Asian patients with psoriasis. Photodermatol Photoimmunol Photomed. 2000;16(5):202-6.

112. Holme SA, Anstey AV. Phototherapy and PUVA photochemotherapy in children. Photodermatol Photoimmunol Photomed. 2004;20(2):69-75.

113. Marqueling AL, Cordoro KM. Systemic treatments for severe pediatric psoriasis: a practical approach. Dermatol Clin. 2013;31(2):267-88.

114. de Jager ME, de Jong EM, van de Kerkhof PC, Seyger MM. Efficacy and safety of treatments for childhood psoriasis: a systematic literature review. J Am Acad Dermatol. 2010;62(6):1013-30.

115. Coven TR, Burack LH, Gilleaudeau R, Keogh M, Ozawa M, Krueger JG. Narrowband UV-B produces superior clinical and histopathological resolution of moderate-to-severe psoriasis in patients compared with broadband UV-B. Arch Dermatol. 1997;133(12):1514-22.

116. Lara-Corrales I, Ramnarine S, Lansang P. Treatment of childhood psoriasis with phototherapy and photochemotherapy. Clin Med Insights Pediatr. 2013;7:25-33.

117. al-Fouzan AS, Nanda A. UVB phototherapy in childhood psoriasis. Pediatr Dermatol. 1995;12(1):66.

118. Jain VK, Aggarwal K, Jain K, Bansal A. Narrow-band UV-B phototherapy in childhood psoriasis. Int J Dermatol. 2007;46(3):320-2.

119. Pasic A, Ceovic R, Lipozencic J, Husar K, Susic SM, Skerlev M, et al. Phototherapy in pediatric patients. Pediatr Dermatol. 2003;20(1):71-7.

120. Tay YK, Morelli JG, Weston WL. Experience with UVB phototherapy in children. Pediatr Dermatol. 1996;13(5):406-9.

121. Diffey BL, Farr PM. The challenge of follow-up in narrowband ultraviolet B phototherapy. Br J Dermatol. 2007;157(2):344-9.

122. Woo WK, McKenna KE. Combination TL01 ultraviolet B phototherapy and topical calcipotriol for psoriasis: a prospective randomized placebo-controlled clinical trial. Br J Dermatol. 2003;149(1):146-50.

123. Behrens S, Grundmann-Kollmann M, Schiener R, Peter RU, Kerscher M. Combination phototherapy of psoriasis with narrow-band UVB irradiation and topical tazarotene gel. J Am Acad Dermatol. 2000;42(3):493-5.

124. Carrozza P, Hausermann P, Nestle FO, Burg G, Boni R. Clinical efficacy of narrow-band UVB (311 nm) combined with dithranol in psoriasis. An open pilot study. Dermatology. 2000;200(1):35-9.

125. Berne B, Blom I, Spangberg S. Enhanced response of psoriasis to UVB therapy after pretreatment with a lubricating base. A single-blind controlled study. Acta Derm Venereol. 1990;70(6):474-7.
126. Wolff K. Side-effects of psoralen photochemotherapy (PUVA). Br J Dermatol. 1990;122 Suppl 36:117-25.
127. Schiener R, Brockow T, Franke A, Salzer B, Peter RU, Resch KL. Bath PUVA and saltwater baths followed by UV-B phototherapy as treatments for psoriasis: a randomized controlled trial. Arch Dermatol. 2007;143(5):586-96.
128. Delrosso G, Bornacina C, Farinelli P, Bellinzona F, Leigheb G, Colombo E. Bath PUVA and psoriasis: is a milder treatment a worse treatment? Dermatology. 2008;216(3):191-3.
129. Wright NA, Piggott CD, Eichenfield LF. The role of biologics and other systemic agents in the treatment of pediatric psoriasis. Semin Cutan Med Surg. 2010;29(1):20-7.
130. Paller AS. Dermatologic uses of methotrexate in children: indications and guidelines. Pediatr Dermatol. 1985;2(3):238-43.
131. Rahman SI, Siegfried E, Flanagan KH, Armbrecht ES. The methotrexate polyglutamate assay supports the efficacy of methotrexate for severe inflammatory skin disease in children. J Am Acad Dermatol. 2014;70(2):252-6.
132. Dervieux T, Orentas Lein D, Marcelletti J, Pischel K, Smith K, Walsh M, et al. HPLC determination of erythrocyte methotrexate polyglutamates after low-dose methotrexate therapy in patients with rheumatoid arthritis. Clin Chem. 2003;49(10):1632-41.
133. Kremer JM, Hamilton RA. The effects of nonsteroidal antiinflammatory drugs on methotrexate (MTX) pharmacokinetics: impairment of renal clearance of MTX at weekly maintenance doses but not at 7.5 mg. J Rheumatol. 1995;22(11):2072-7.
134. Wallace CA, Smith AL, Sherry DD. Pilot investigation of naproxen/methotrexate interaction in patients with juvenile rheumatoid arthritis. J Rheumatol. 1993;20(10):1764-8.
135. Thomas DR, Dover JS, Camp RD. Pancytopenia induced by the interaction between methotrexate and trimethoprim-sulfamethoxazole. J Am Acad Dermatol. 1987;17(6):1055-6.

136. Lee CS, Koo J. A review of acitretin, a systemic retinoid for the treatment of psoriasis. Expert Opin Pharmacother. 2005;6(10):1725-34.
137. Pereira TM, Vieira AP, Fernandes JC, Sousa-Basto A. Cyclosporin A treatment in severe childhood psoriasis. J Eur Acad Dermatol Venereol. 2006;20(6):651-6.
138. Alli N, Gungor E, Karakayali G, Lenk N, Artuz F. The use of cyclosporin in a child with generalized pustular psoriasis. Br J Dermatol. 1998;139(4):754-5.
139. Perrett CM, Ilchyshyn A, Berth-Jones J. Cyclosporin in childhood psoriasis. J Dermatolog Treat. 2003;14(2):113-8.
140. Mahe E, Bodemer C, Pruszkowski A, Teillac-Hamel D, de Prost Y. Cyclosporine in childhood psoriasis. Arch Dermatol. 2001;137(11):1532-3.
141. Kilic SS, Hacimustafaoglu M, Celebi S, Karadeniz A, Ildirim I. Low dose cyclosporin A treatment in generalized pustular psoriasis. Pediatr Dermatol. 2001;18(3):246-8.
142. Kim HS, Kim GM, Kim SY. Two-stage therapy for childhood generalized pustular psoriasis: low-dose cyclosporin for induction and maintenance with acitretin/narrowband ultraviolet B phototherapy. Pediatr Dermatol. 2006;23(3):306-8.
143. Hashkes PJ, Uziel Y, Laxer RM. The safety profile of biologic therapies for juvenile idiopathic arthritis. Nat Rev Rheumatol. 2010;6(10):561-71.
144. Hawrot AC, Metry DW, Theos AJ, Levy ML. Etanercept for psoriasis in the pediatric population: experience in nine patients. Pediatr Dermatol. 2006;23(1):67-71.
145. Papoutsaki M, Costanzo A, Mazzotta A, Gramiccia T, Soda R, Chimenti S. Etanercept for the treatment of severe childhood psoriasis. Br J Dermatol. 2006;154(1):181-3.
146. Paller AS, Siegfried EC, Langley RG, Gottlieb AB, Pariser D, Landells I, et al. Etanercept treatment for children and adolescents with plaque psoriasis. N Engl J Med. 2008;358(3):241-51.
147. European Medicines Agency. Human Medicines - CHMP post-authorisation summary of positive opinion for Enbrel [cited 2016 April 15]. Available from: http://www.ema.europa.eu/ema/index.jsp%3Fcurl%3dpages/medicines/human/medicines/000262/smops/Positive/human_smop_000264.jsp&mid%3dWC0b01ac058001d127&murl%3dmenus/medicines/medicines.jsp.

148. European Medicines Agency. Human Medicines - Remicade Therapeutic Indication [cited 2016 April 15]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000240/human_med_001023.jsp&mid=WC0b01ac058001d124.

149. European Medicines Agency. Human Medicines - CHMP post-authorisation summary of positive opinion for Humira [cited 2016 April 15]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000481/smops/Positive/human_smop_000940.jsp&mid=WC0b01ac058001d127.

150. Malkonen T, Wikstrom A, Heiskanen K, Merras-Salmio L, Mustonen H, Sipponen T, et al. Skin reactions during anti-TNFalpha therapy for pediatric inflammatory bowel disease: a 2-year prospective study. Inflamm Bowel Dis. 2014;20(8):1309-15.

151. Kimball AB, Gordon KB, Fakharzadeh S, Yeilding N, Szapary PO, Schenkel B, et al. Long-term efficacy of ustekinumab in patients with moderate-to-severe psoriasis: results from the PHOENIX 1 trial through up to 3 years. Br J Dermatol. 2012;166(4):861-72.

152. Kimball AB, Gordon KB, Langley RG, Menter A, Chartash EK, Valdes J, et al. Safety and efficacy of ABT-874, a fully human interleukin 12/23 monoclonal antibody, in the treatment of moderate to severe chronic plaque psoriasis: results of a randomized, placebo-controlled, phase 2 trial. Arch Dermatol. 2008;144(2):200-7.

153. Gordon KB, Papp KA, Langley RG, Ho V, Kimball AB, Guzzo C, et al. Long-term safety experience of ustekinumab in patients with moderate to severe psoriasis (Part II of II): results from analyses of infections and malignancy from pooled phase II and III clinical trials. J Am Acad Dermatol. 2012;66(5):742-51.

154. European Medicines Agency. Human Medicines - Stelara: EPAR - Product Information [cited 2016 April 15]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000958/WC500058513.pdf.

155. Landells I, Marano C, Hsu MC, Li S, Zhu Y, Eichenfield LF, et al. Ustekinumab in adolescent patients age 12 to 17 years with moderate-to-severe plaque psoriasis: results of the randomized phase 3 CADMUS study. J Am Acad Dermatol. 2015;73(4):594-603.